

The Examiner alleges that the term

“the peptide factor is modified such that at least one murine epidermal growth factor tyrosine amino acid residue is substituted with a tyrosine analogue or at least one murine epidermal growth factor arginine amino acid residue is substituted with an arginine analogue”

is unclear, as it does not indicate what else is modified in the peptide factor comprising amino acid residues 33 to 42 of murine epidermal growth factor besides the modification of at least one murine epidermal growth factor Tyrosine or Arginine residue by a Tyrosine or Arginine analogue.

The second paragraph of 35 U.S.C. § 112 requires that the claims set out and circumscribe a particular area with a reasonable degree of precision and particularity. In making this determination the claims must be analysed in light of the teachings of the prior art and what those skilled in the art would understand when the claim is read in the light of the specification.

The Examiner's action with respect to claims 1 to 18 has not set forth a *prima facie* rejection under 35 U.S.C. § 112, second paragraph. The primary purpose of § 112, second paragraph, is to “ensure that the scope of the claims is clear so that the public is informed of the boundaries of what constitutes infringement of the patent”. MPEP § 2173. Essentially, a § 112, second paragraph rejection seeks to identify and correct ambiguity of claim language or grammatical structure so that the recited scope of the invention is clear to one skilled in the art. Such a rejection is never properly directed to the substance of the claimed invention, but only to the linguistic form of the claim. The sole inquiry under § 112, second paragraph, is whether the public would be informed of the boundaries of what constitutes infringement should the claim in question be granted.

It is well-established that “[b]readth of a claim is not to be equated with indefiniteness.” *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971); MPEP § 2173.04.

"If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. § 112, second paragraph." § 2173.04.

Examiner has not explained why one skilled in the art would not understand the boundaries of the invention as defined by claim 1. Examiner has not explained why one skilled in the art would fail to understand the meaning of any term set forth in claim 1, or the scope of any individual element in claim 1. Indeed, the principal elements of claim 1 have been defined in the specification. Indeed, every term contained in claim 1 which is subject to definition is *defined in the specification*.

Applicant submits that the scope of claim 1 as amended in response to the Examiner's first Office Action clearly sets out the essential elements of the invention namely;

- ◆ A peptide factor based on residues 33 to 42 of murine epidermal growth factor
- ◆ Modified to include at least one modification selected from
  - a) a tyrosine analogue in substitution of at least one murine epidermal growth factor tyrosine amino acid, and
  - b) an arginine analogue in substitution of at least one murine epidermal growth factor arginine amino acid.

The specification of the Application clearly sets out that residues 33 to 42 of murine epidermal growth factor can be modified from the natural sequence to protect the peptide factor from protease attack (e.g., see page 2, lines 24 to 25 of the substitute specification). Preferred modifications are taught as being conferred by substitution of tyrosine at position 5 with a tyrosine analogue and/or substitution of arginine at position 9 with an arginine analogue. Examples of tyrosine analogues, such as TIC-OH, 2', 6'-dimethyl-beta-methyl-tyrosine, 2-O-methyl and 2-O-ethyl-tyrosine and the like are given on e.g. page 3 line 2 and page 3 line 11 to page 4 line 2. Examples of suitable arginine

analogues such as citrulline, cysteine derived analogues, thiono-citrulline and homo-glutamine are provided on page 3.

Applicant submits that the mere breadth of claim 1 does not in itself make the claim indefinite. Claim 1 clearly indicates the essential elements of the present invention and thus metes and the bounds of claim 1 would be clear to one skilled in the art. The Application as filed clearly discloses a method for making the invention as claimed in claim 1 and further provides details of further modifications which could be made in addition to substitution of tyrosine and/or arginine residues as described above. For example, the specification teaches that the peptides may be protected by proteolytic degradation by substitution of key residues with unnatural amino acid analogues at susceptible bonds, and may be capped at the *N*- terminal with an acetyl group, at the *C*-terminal with an amide group and at the thiol groups of cysteines with acetamido methyl group (see page 2 lines 15-19, 24-30 of the substitute specification). Further suitable modifications, such as the replacement of susceptible peptide bonds with protease resistant peptide bond isosteres, replacement of a glycine residue with  $\alpha\alpha$ -dialkyl substituted amino acid, and stabilisation of a helical turn of the peptide using suitable intra chain linkers are described on page 4 lines 11 to 31 of the substitute specification. The claim requires that the peptide factor binds to laminin receptors. A suitable laminin attachment assay is described which can be used for testing the binding of a peptide factor to a laminin receptor.

Applicant respectively submits that claim 1 clearly sets out the essential elements of the present invention with a reasonable degree of precision and particularity i.e. that at least one murine epidermal growth factor tyrosine amino acid residue is substituted with a tyrosine analogue or at least one murine epidermal growth factor arginine amino acid residue is substituted with an arginine analogue and, moreover, provides adequate teaching on how to test factors for binding to laminin receptors. The skilled person will readily understand the metes and bounds of the claim when read in light of the teaching of the specification and the general knowledge in the field.

Reconsideration and withdrawal of the 35 U.S.C. § 112, second paragraph, rejection of claims 1 to 18 is earnestly solicited.

The Examiner's objection to Claims 5 and 6 has been addressed by amendment to include the step of binding a laminin receptor. Some further minor modifications have been made to the claims to further clarify their meaning.

The Examiner's objection to claim 7 has been addressed by amendment of the claim to delete reference to "an antagonist" and to further clarify the claim.

Amendments have also been made to Claim 8 to further clarify its meaning, correct an incorrect claim dependency and to correct a typographical error by replacement of "immaturity" by "prematurity".

The Examiner's objection to claim 11 has been addressed by cancellation of claim

The Examiner's objections to claims 13, 14, 16 and 17 have been addressed by amendment of these claims to properly recite the "method".

It is submitted that with these amendments the claims comply with 35 U.S.C. § 112.

#### **New Claims**

New Claims 19 to 24 have been added. No new matter has been added with those claims in that support for the claims can be found in the claims and specification as filed.

Claim 19 is based on pending claim 1, but includes the feature that modifications further to the modification to the tyrosine or arginine residues are selected from the group consisting of: chemical modification of the N terminal of the murine epidermal growth factor by the addition of an amino acid capping moiety; chemical modification of the C terminal of the murine epidermal growth factor amino acid residue by the addition

of an amino acid capping moiety; chemical modification of a murine epidermal growth factor cysteine residue thiol group by the addition of an amino acid capping moiety to the cysteine residue thiol group; replacement of a peptide bond with a protease-resistant peptide bond isostere, replacement of a glycine residue with  $\alpha\alpha$ -dialkyl substituted amino acid; and stabilisation of a helical turn of the peptide using suitable intra chain linkers.

New claim 20 is dependent on claim 19 and recites the additional limitation that the peptide factor includes at least one of the further modifications recited in that claim.

New claim 21 is based on original claim 1 but includes the limitation that the only modification which can be made to residues 33 to 42 of the murine EGF is the recited substitution of the tyrosine and/or arginine residues.

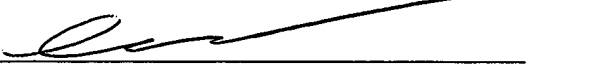
New claims 22, 23 correspond to original claims 3 and 4 respectively but are dependent on claim 19. Claims 24 and 25 correspond to claim 4, but include the limitations of the peptide factor as recited in claim 19. Claims 26 and 27 correspond to claims 7 and 8, but depend on claim 25.

Conclusion

Based on the foregoing, all claims are believed to be in condition for allowance. An early and favorable action toward that end is earnestly solicited.

Respectfully submitted,

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**Appendix A- “Marked-up” Version of Amended Claims as Required under 37 C.F.R. 1.121(c)(1)(ii)**

5. (twice amended) A method of binding to a laminin receptor as an antagonist, the method comprising [preparing] the steps of:

a) administering a medicament comprising a peptide factor comprising amino acid residues 33 to 42 of murine epidermal growth factor wherein the peptide factor is modified such that at least one murine epidermal growth factor tyrosine amino acid residue is substituted with a tyrosine analogue or at least one murine epidermal growth factor arginine amino acid residue is substituted with an arginine analogue, and

b) binding the peptide factor to the laminin receptor.

6. (twice amended) A method of binding to a laminin receptor as an agonist, the method comprising [preparing] the steps of:

a) administering a medicament comprising a peptide factor comprising amino acid residues 33 to 42 of murine epidermal growth factor wherein the peptide factor is modified such that at least one murine epidermal growth factor tyrosine amino acid residue is substituted with a tyrosine analogue or at least one murine epidermal growth factor arginine amino acid residue is substituted with an arginine analogue, and

b) binding the peptide factor to the laminin receptor.

7. (twice amended) The method of claim 6 wherein [the preparation of the] said medicament is [used to treat] for treating endothelial cell wounding.

8. (twice amended) The method according to claim [5] 6 wherein [the preparation of the] said medicament is [used to treat] for treating retinopathy of [immaturity] prematurity.

13. (once amended) The [peptide factor] method of claim 12, wherein the murine epidermal growth factor tyrosine residue is substituted by tetrahydroisoquinoline-3-carboxylic acid.
14. (once amended) The [peptide factor] method of claim 12 wherein the murine epidermal growth factor arginine residue is substituted by Citrulline.
16. (once amended) The [peptide factor] method of claim 15, wherein the murine epidermal growth factor tyrosine residue is substituted by tetrahydroisoquinoline-3-carboxylic acid.
17. (once amended) The [peptide factor] method of claim 15 wherein the murine epidermal growth factor arginine residue is substituted by Citrulline.
18. (once amended) The method of claim [6] 15 wherein said medicament is for treatment of retinopathy of [immaturity] prematurity.